

WHAT IS CLAIMED IS:

1 1. A nucleic acid encoding a MCOLN1 polypeptide, wherein a mutation of a
2 *MCOLN1* gene encoding the MCOLN1 polypeptide results in a defect in expression of a
3 functional MCOLN1, wherein the nucleic acid shares at least about 95% sequence identity with a
4 corresponding sequence from SEQ ID NO: 1 or SEQ ID No: 2.

1 2. The nucleic acid of claim 1, wherein the mutation is selected from the
2 group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a
3 nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

1 3. The nucleic acid of claim 1, wherein the mutation is selected from the
2 group consisting of:

- 3 (a) an A to G substitution at position 5534 (SEQ ID NO:1);
4 (b) a deletion from nucleotide 511 to nucleotide 6944 (SEQ ID NO:1);
5 (c) an insertion of T between nucleotide numbers 1334 and 1335 (SEQ ID NO:2);
6 (d) a deletion of CTT 1346-1348 (SEQ ID NO:2);
7 (e) an A to G substitution a position 9107 (SEQ ID NO:1);
8 (f) a G to T substitution at position 1461 (SEQ ID NO:2);
9 (g) a C to T substitution at position 429 (SEQ ID NO:2);
10 (h) a G to T substitution at position 1209 (SEQ ID NO:2);
11 (i) a CC deletion at 598-599 (SEQ ID NO:2); and
12 (j) a C to T substitution at position 639 (SEQ ID NO:2).

1 4. The nucleic acid of claim 1, wherein the defect in expression of a
2 functional MCOLN1 results in development of mucopolipidosis IV.

1 5. The nucleic acid of claim 1, which encodes a MCOLN1 polypeptide
2 having an amino acid sequence at least about 95% identical to SEQ ID NO:3.

1 6. The nucleic acid of claim 5, wherein the polypeptide has an amino acid
2 sequence as depicted in SEQ ID NO:3.

1 7. The nucleic acid of claim 6 which has a nucleotide sequence as depicted in
2 SEQ ID NO:1 or SEQ ID NO:2.

1 8. A MCOLN1 polypeptide which has an amino acid sequence at least about
2 95% identical to SEQ ID NO: 3.

1 9. MCOLN1 polypeptide of claim 8, wherein the polypeptide has the amino
2 acid sequence of SEQ ID NO:3 comprising a mutation selected from the group consisting of
3 deletion of residue 408, deletion of residues 454 to 469; a Val to Leu substitution at residue 446;
4 an Arg to X[?] substitution at residue 102; an Asp to Thr substitution at residue 362; and an Arg
5 to X[?] substitution at residue 172.

1 10. The MCOLN1 polypeptide of claim 8 which has an amino acid sequence
2 as depicted in SEQ ID NO:3.

1 11. An antibody that binds specifically to the MCOLN1 polypeptide of claim
2 8.

1 12. A method for detecting a genetic mutation associated with a mucopolipidosis
2 in a mammal, which method comprises detecting a mutation in a gene for MCOLN1, wherein the
3 gene for MCOLN1 has a sequence at least 95% identical to SEQ ID NO:1.

1 13. The method according to claim 12, wherein the mutation is selected from
2 the group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a
3 nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

1 14. The method according to claim 13, wherein the mutation is selected from
2 the group consisting of:

- 3 (a) an A to G substitution at position 5534 (SEQ ID NO:1);
- 4 (b) a deletion from nucleotide 511 to nucleotide 6944 (SEQ ID NO:1);
- 5 (c) an insertion of T between nucleotide numbers 1334 and 1335 (SEQ ID NO:2);
- 6 (d) a deletion of CTT 1346-1348 (SEQ ID NO:2);
- 7 (e) an A to G substitution a position 9107 (SEQ ID NO:1);
- 8 (f) a G to T substitution at position 1461 (SEQ ID NO:2);
- 9 (g) a C to T substitution at position 429 (SEQ ID NO:2);
- 10 (h) a G to T substitution at position 1209 (SEQ ID NO:2);
- 11 (i) a CC deletion at 598-599 (SEQ ID NO:2); and
- 12 (j) a C to T substitution at position 639 (SEQ ID NO:2).

1 15. The method according to claim 12, wherein the mucopolipidosis is
2 mucopolipidosis IV.

1 16. A method for diagnosing a mucopolipidosis, which method comprises
2 detecting a mutation in a gene for MCOLN1 that results in a defect in expression of a functional
3 MCOLN1, wherein the gene for MCOLN1 has a sequence at least 95% identical to SEQ ID
4 NO:1.

1 17. The method according to claim 16, wherein the mutation is selected from
2 the group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a
3 nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

1 18. The method according to claim 17, wherein the mutation is selected from
2 the group consisting of:

- 3 (a) an A to G substitution at position 5534 (SEQ ID NO:1);
- 4 (b) a deletion from nucleotide 511 to nucleotide 6944 (SEQ ID NO:1);
- 5 (c) an insertion of T between nucleotide numbers 1334 and 1335 (SEQ ID NO:2);
- 6 (d) a deletion of CTT 1346-1348 (SEQ ID NO:2);
- 7 (e) an A to G substitution a position 9107 (SEQ ID NO:1);
- 8 (f) a G to T substitution at position 1461 (SEQ ID NO:2);
- 9 (g) a C to T substitution at position 429 (SEQ ID NO:2);
- 10 (h) a G to T substitution at position 1209 (SEQ ID NO:2);
- 11 (i) a CC deletion at 598-599 (SEQ ID NO:2); and
- 12 (j) a C to T substitution at position 639 (SEQ ID NO:2).

1 19. The method according to claim 16, wherein the mucopolipidosis is MLIV.

1 ~~20.~~ A method for predicting the likelihood of developing MLIV comprising
2 detecting a mutation in a gene for MCOLN1 that results in a defect in expression of a functional
3 MCOLN1, and determining that there is a likelihood of developing MLIV if the mutation is
4 present, wherein the gene for MCOLN4 has a sequence at least 95% identical to SEQ ID NO:1.

1 21. The method according to claim 20, wherein the mutation is selected from
2 the group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a
3 nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

1 22. The method according to claim 21, wherein the mutation is selected from
2 the group consisting of:

- 3 (a) an A to G substitution at position 5534 (SEQ ID NO:1);
- 4 (b) a deletion from nucleotide 511 to nucleotide 6944 (SEQ ID NO:1);

- (c) an insertion of T between nucleotide numbers 1334 and 1335 (SEQ ID NO:2);
- (d) a deletion of CTT 1346-1348 (SEQ ID NO:2);
- (e) an A to G substitution a position 9107 (SEQ ID NO:1);
- (f) a G to T substitution at position 1461 (SEQ ID NO:2);
- (g) a C to T substitution at position 429 (SEQ ID NO:2);
- (h) a G to T substitution at position 1209 (SEQ ID NO:2);
- (i) a CC deletion at 598-599 (SEQ ID NO:2); and
- (j) a C to T substitution at position 639 (SEQ ID NO:2).

23. A kit for detecting a genetic mutation in a gene for MCOLN1 that results in a defect in expression of a functional MCOLN1, comprising an oligonucleotide that specifically hybridizes to or adjacent to a site of a mutation of the gene for MCOLN1 that results in a defect in expression of a functional MCOLN1, wherein the gene for MCOLN1 has a sequence at least 95% identical to SEQ ID NO:1.

24. The kit according to claim 23, wherein the oligonucleotide is a labeled probe having a sequence corresponding to the sequence of the gene encoding MCOLN1 at the site of the mutation, whereby hybridization of the probe is indicative of the presence of the mutation.

25. The kit according to claim 23, wherein the oligonucleotide hybridizes to a first site adjacent to the site of the mutation, further comprising a second oligonucleotide that specifically hybridizes to a second site adjacent to the site of the mutation, wherein the second site is on the opposite strand relative to the first site, and oriented relative to the first site such that both sites flank opposite sides of the site of the mutation, whereby the first and second oligonucleotides serve as primers for PCR amplification of the site of the mutation.

1 26. The kit according to claim 23, wherein the mutation is selected from the
2 group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a
3 nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

1 27. The kit according to claim 26, wherein the mutation is selected from the
2 group consisting of:

- 3 (a) an A to G substitution at position 5534 (SEQ ID NO:1);
4 (b) a deletion from nucleotide 511 to nucleotide 6944 (SEQ ID NO:1);
5 (c) an insertion of T between nucleotide numbers 1334 and 1335 (SEQ ID NO:2);
6 (d) a deletion of CTT 1346-1348 (SEQ ID NO:2);
7 (e) an A to G substitution a position 9107 (SEQ ID NO:1);
8 (f) a G to T substitution at position 1461 (SEQ ID NO:2);
9 (g) a C to T substitution at position 429 (SEQ ID NO:2);
10 (h) a G to T substitution at position 1209 (SEQ ID NO:2);
11 (i) a CC deletion at 598-599 (SEQ ID NO:2); and
12 (j) a C to T substitution at position 639 (SEQ ID NO:2).

1 28. A kit for detecting a genetic mutation in a gene for MCOLN1 that results
2 in a defect in expression of a functional MCOLN1 polypeptide, comprising the antibody of claim
3 11 and a detector of antibody binding.

1 29. A method of treating a mucopolidosis or ion channel defect in a subject
2 suffering from mucopolidosis or ion channel defect, which method comprises administering an
3 amount of a vector that expresses a nucleic acid encoding functional MCOLN1 effective to
4 express a functional level of MCOLN1 into cells of the subject, wherein at least the functional
5 MCOLN1 has an amino acid sequence that is at least about 95% identical to SEQ ID NO:3.

1 30. The method according to claim 29 wherein the MCOLN1 has an amino
2 acid sequence as depicted in SEQ ID NO:3.

1 31. The method according to claim 29, wherein the mucopolidosis results from
2 a mutation in a gene for MCOLN1 that results in a defect in expression of MCOLN1.

1 32. The method according to claim 29, wherein the mucopolidosis is MLIV.

1 ~~33.~~ An expression vector comprising a gene encoding functional human
2 MCOLN1 operatively associated with a promoter, wherein the functional MCOLN1 has an
3 amino acid sequence that is at least about 95% identical to SEQ ID NO:3.

1 34. The expression vector of claim 33, wherein the functional MCOLN1 has
2 an amino acid sequence as depicted in SEQ ID NO:3.

1 35. A pharmaceutical composition comprising the expression vector of claim
2 33 and a pharmaceutically acceptable carrier or excipient.

1 36. A method of screening for a candidate compound that modulates activity
2 of MCOLN1, which method comprises detecting binding of MCOLN1 with a compound and
3 isolating the compound, wherein the functional MCOLN1 has an amino acid sequence that is at
4 least about 95% identical to SEQ ID NO:3.

1 37. The method according to claim 36, wherein the MCOLN1 is a mutant
2 form of MCOLN1.

1 38. The method according to claim 36, wherein the functional MCOLN1 has
2 an amino acid sequence as depicted in SEQ ID NO:3.
3